Imatinib mesylate has been reported to produce positive results in atypical chronic myeloproliferative disorders (CMD) with chromosomal translocations that disrupt the platelet-derived growth factor receptor β gene (PDGFRB). We used imatinib to treat a 49-year-old man with atypical CMD in accelerated phase and the H4-PDGFRB fusion gene. After 3 months of treatment, we observed grade 4 hematologic toxicity and a lack of response.

In September 1999, a 49-year-old man presented with asthenia and huge splenomegaly. Blood counts performed 2 years previously had already shown hyperleukocytosis and eosinophilia that were not investigated. The blood count at presentation showed hemoglobin 68 g/L, white blood cell count (WBC) of 7.4×10⁹/L with 64% neutrophils, 19% lymphocytes, 6% monocytes, 6% eosinophils, 1% basophils, 2% metamyelocytes, 1% myelocytes, 1% promyelocytes, 1% erythroblasts and a platelet count of 63×10⁹/L. Bone marrow aspiration was difficult and showed granulocytic hyperplasia without excess of blast cells and few megakaryocytes. The bone marrow biopsy, stained with hematoxylin–eosin and May–Grünwald Giemsa, showed granulocytic hyperplasia, established myelofibrosis (grade III reticulin) and no evidence of blast transformation. Cyto genetic analysis on bone marrow cells showed: 46,XY, t(5;10) [q33;p13] [18]/46,XY [2]. Reverse transcription polymerase chain reaction (RT-PCR) did not detect β-actin (ABL). RT-PCR to detect the H4-PDGFRB fusion gene was performed on bone marrow cells as previously described. The fusion junction was identical to that found in the two previously reported cases (Figure 1). The patient was given hydroxyurea which controlled the leukocytosis but the anemia and thrombocytopenia worsened. The spleen enlarged and a splenectomy was performed. The in vitro sensitivity of mononuclear (MN) cells to imatinib was studied. Bone marrow MN cells were cultured as previously reported and compared to CML cells. The viability of MN cells exposed or not to 1 µM of imatinib was determined and found to be 50% versus 70% at day 2 and 35% versus 55% at day 3. It should, however, be noted that 100% of cells were dead by the 6th day of culture in the presence or absence of imatinib (Figure 2). In February 2002, the patient began therapy with imatinib mesylate at 400 mg daily. At this time cytogenetics analysis showed additional abnormalities of t(5;10) in 2 mitoses: add(3)(p21) and monosomy 15.

Imatinib was stopped after 3 months of therapy because of severe hematologic toxicity with the patient requiring platelet and red blood cell transfusions. In the six months following discontinuation of imatinib, hematologic recovery was observed. A second trial of imatinib immediately led to a worsening of thrombocytopenia. Imatinib was definitively stopped and blood counts again recovered. Cyto genetic analysis, repeated after each course of imatinib, showed the persistence of t(5;10) in all the mitoses and H4-PDGFRB transcript was still detectable by RT-PCR. Hydroxyurea was subsequently given with persisting good hematologic control until now.

Abnormal activation of PDGFRB was first described as a consequence of the t(5;12)(q33;p13), which fuses the 5’end of ETv6 to the 3’end of PDGFRB including the entire tyrosine kinase domain, and complete and durable responses to imatinib were reported in four patients with t(5;12) translocation. Other translocations involving the same region of PDGFRB have been reported, t(5;10) (q33;q21) translocation fusing PDGFRB to H4(D10S170), a gene encoding for a 585-amino acid protein with no significant homology to known genes and with unknown function, has been reported in 3 patients. H4 is fused to the ret gene as a result of an inv(10)(q22q21) in a subset of papillary thyroid carcinomas. The H4-ret fusion protein is a constitutively active tyrosine kinase.
One patient with a t(5;10) was treated at diagnosis with imatinib and achieved clinical and cytogenetic responses after 3 weeks. In contrast our patient did not respond to imatinib. It must be noted that in our case treatment with imatinib was begun 29 months after diagnosis and 5 years of treatment with imatinib suggested that the patient had an accelerated phase of disease. Imatinib was given at the dose of 400 mg/day, which is lower than the dose recommended for accelerated phase CML. Some CML patients have imatinib-resistant disease as a consequence of acquired mutations in the ATP binding pocket of BCR-ABL. Direct sequencing of the H4-PDGFRB kinase domain (corresponding to amino acids 478-886 of PDGFRB) was performed. The sequence of the kinase domain showed no coding changes. We hypothesize that other mechanisms of resistance were responsible for the lack of response observed in our patient. Drugs with activity against the imatinib-resistant variants are currently being developed and will be therapeutically important.10

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Chronic Myeloproliferative Disorders

The effects of hydroxyurea on PRV-1 expression in patients with essential thrombocythemia and polycythemia vera

The study was designed to investigate the influence of hydroxyurea (HU) treatment on PRV-1 expression. Eighteen newly diagnosed patients with essential thrombocythemia (ET) or polycythemia vera (PV) were included. HU significantly increased PRV-1 gene expression in the early stage of treatment.

References